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(54) Title: METHOD FOR AMELIORATION OF SOCIAL PHOBIA

(57) Abstract

A method is provided that is suitable for treating patients having disorders such as social phobia. The method comprises the steps of identifying a patient suffering from social phobia and treating the patient with a therapeutically effective dose of a dopaminergic agonist such as apomorphine hydrochloride.

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METHOD FOR AMELIORATION OF SOCIAL PHOBIA

TECHNICAL FIELD

The invention relates to the pharmacological treatment of phobias, and in particular, social phobia.

BACKGROUND OF THE INVENTION

Social phobia is an unreasonable, marked and persistent fear of one or more social or performance situations in which a person is exposed to unfamiliar people or to possible scrutiny by others.

Victims of social phobia fear attending social functions, meetings, especially among new or unfamiliar persons, formal performance situations, and assertiveness situations. Public speaking or performance are especially likely to elicit social phobia behavior. Academic testing and the failure to perform well on testing has been associated with social phobia.

Social phobia, also known as social anxiety disorder, is a common psychological problem which on occasion involves or may involve physiological manifestations. Clinically, social phobia may be misdiagnosed since many of the physiological manifestations are similar to those of other psychological disorders. For example, physical symptoms, which may include sweating, shaking, palpitations, nausea and diarrhea are occurrences reported in patients suffering from social phobia, and may be thought to arise from other illnesses. However, compared to patients with panic disorder, patients with social phobia tend to have a greater frequency of blushing, muscle twitching, stammering, and dry mouth, and a lower incidence of dizziness or respiratory symptoms.

The defining criteria for a diagnosis of social phobia are found in: American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th ed., ("DSM IV") APA Press, Washington, D.C. (1994), pp. 416-417, which is explicitly incorporated herein by reference.

The hallmark of social phobia is its cognitive features, specifically the negative evaluation and fears of humiliation and/or embarrassment. This fear is most obviously expressed as a "fear of saying the wrong thing" or speaking awkwardly. Generalization of this fear includes concerns the patient may show symptoms of anxiety, twitches, spilling things, as well as the anticipation of these fears. A very specific situation or circumstance may elicit the fear, such as taking a test or speaking to a group of three or more persons. Alternatively, a global set of fears may affect a significant part of the patient's waking hours. Further complicating the disorder is the overlay of other disorders, for example, the co-morbidity of social phobia with alcohol or drug abuse, anxiety disorders, secondary depression, and suicidal ideation.

Victims of social phobia fear and avoid situations in which they are exposed to the scrutiny of other people because of their fear of acting in an embarrassing way. A national survey of more than 8000 individuals reported a lifetime prevalence of 13.3% for social phobia. Magee, W.J., et al., Agoraphobia, Simple Phobia, and Social Phobia in the National Comorbidity Survey, Arch. Gen. Psychiatry, 53:159-168. Social phobia causes significant role impairment in 33.5% of its victims. Id. at 164. Social phobia has been treated with drugs, behavioral therapy or a combination pharmaceutical and behavioral approach, with mixed results. There is no single drug approved for the treatment of social phobia. What is needed is a drug effective for the treatment of social phobia.

Cognitive processing by a person suffering from social phobia is characterized by a large amount of negative thoughts correlated to the levels of anxiety and phobic severity. Dodge, C.S., et al., Daily heterosocial interactions of high and low socially anxious college students, Behavior Therapy, **18:** 90-96 (1987). The victim of social phobia may also experience physical symptoms characteristic of autonomic nervous system activation: dry mouth, blushing, palpitations, sweating, trembling and nausea. A social phobic attack may also include other physical symptoms such as twitching and stammering.

Social phobia may be focused or generalized. In focused cases, the person usually fears a specific discrete setting, i.e., performance anxiety or stage fright. Generalized social phobia relates to a fear of most social situations. Because of the anticipatory nature of these events, anxiety can overwhelm the patient, rendering him unable to perform social obligations.

The diagnosis of the social phobia begins with a physiological and psychological assessment of the patient. However, the problem in establishing a diagnosis of social phobia is the issue of diagnostic thresholds.

Distinguishing social phobia from normal shyness is a quantitative issue related to the level of distress and impairment associated with social fears. Because shyness is usually self-defined, it probably represents a more heterogeneous category than social phobia, including cases that would not meet clinical criteria for the social phobia. In a recent telephone survey of a community sample, Stein and coworkers examined the effects of different thresholds for diagnosis of social anxiety. Stein, M.B., et al., Setting diagnostic thresholds for social phobia: Consideration from a community survey of social anxiety, Amer. J. Psychiatry, **151:** 408-412 (1994). Different diagnostic thresholds led to variations in prevalence from 1.9% to 18.7%, depending on the stringency of the definitions of distress and impairment.

At the other end of the severity spectrum, another problem in differential diagnosis is possible overlap of social phobia and avoidant personality

disorder. Avoidant personality disorder as defined in the DSM-IV appears to be a more severe form of social phobia, but groups of patients have not been found to differ qualitatively in any substantive way. Schneier, F.R., Clinical assessment strategies for social phobia, Psychiatric Annals, **25:** 550-553 (1995). Rather than trying to differentiate between both disorders, it is more useful to code a diagnosis of social phobia in Axis I and a diagnosis of avoidant personality disorder in Axis II, where warranted.

One current behavioral treatment for social phobia is cognitive-behavioral therapy, as exemplified by the cognitive-behavioral group treatment (CBGT) developed by Heimberg and associates. Heimberg, R.G., et al., Cognitive-behavioral group treatment of social phobia: Comparison to a credible placebo control, Cognitive Therapy Research, **14:** 1-23 (1990). This has been one of the most widely studied and empirically supported psychosocial treatments for social phobia. CBGT combines (1) cognitive restructuring techniques; (2) exposure within sessions; and (3) instructions to patients to practice these techniques between sessions in their daily lives. The group is a source of support for its members and provides them with opportunities for exposure to several feared situations such as introductions and public speaking. While behavioral therapy for social phobia is often administered in a group format, individual cognitive-behavior therapy also appears effective.

In contrast with the growing literature documenting the effectiveness of cognitive-behavioral treatment of social phobia, psychodynamic and supportive approaches remain untested. Given the lack of evidence for their utility, these approaches cannot be considered first-line treatments for social phobia at present. Clinical experience suggests, however, that these approaches are helpful in some cases, and an understanding of the psychodynamic and developmental vicissitudes of the patients may also be useful in tailoring exposure exercises to individual patients. A risk of nondirective therapies is to inadvertently enable the social avoidance by emphasizing the search for insight over corrective action. Schneier, F.R., et al., Diagnosis and treatment of social phobia, J. Practical Psychiatry and Behavioral Health, **2:** 94-104 (1996).

No drugs are currently approved by the Food and Drug Administration (FDA) for the treatment of social phobia. Until 1985 little was known about the psychopharmacotherapy of social phobia. Leibowitz, M.R., et al., Social phobia: Review of a neglected anxiety disorder, Arch. Gen. Psychiatry, **42:** 729-736 (1985). At present there is evidence that a number of drugs may be useful in the treatment of this disorder.

Tricyclic antidepressants and clonidine have been used occasionally for treating social phobia, but their efficacy is uncertain. Efficacy of bupropion is reported for a single case, although others have reported negative results in a limited number of patients. den Boer, J.A., et al., Recent advances in the psychopharmacology of social phobia, Prog. Neuropyschopharmacol. Biol. Psychiatry, **18:** 625-645 (1994). However, this case reports of efficacy of buproprion is difficult to assess because the case is complicated by the presence of comorbid depression in the patient. Clark, D.B. & Agras, W.S., The assessment and treatment of anxiety performance in musicians, Amer. J. Psychiatry, **152:** 1368-1371 (1991).

Neurobiology of Social Phobia.

In the absence of definitive data demonstrating the neurobiological mechanisms underlying social phobia, the theories of treatment have two bases: observations made during pharmacotherapy of which empirical drug treatments are purportedly effective, and the results of experiments on corresponding animal models. While a diverse range of drug therapies have been tried with various efficacies, the results of experiments on animal models have led to the present invention.

Neurobiology of Social Phobia: Observations from Pharmacotherapy.

Alcohol has played an informal role in the pharmacotherapy of social discomfort for centuries. Jefferson, J.W., Social Phobia: A Pharmacologic Treatment Overview, J. Clin. Psychiatry, **56 (Suppl. 5):** 18-24 (1995). The substantial comorbidity of alcohol abuse and social phobia may reflect a role in the self-medication of social phobics. Id. However, alcohol abuse has not been suggested as an acceptable drug therapy for social phobia.

β-adrenergic receptor blocking agents ("beta-blockers") have been reported to be effective in a special form of social phobia, performance anxiety. Since not all beta-blockers effectively cross the blood-brain barrier, it may be that the efficacy of beta-blockers in performance anxiety is due to a reduction in autonomic symptoms such as palpitations and tremors, and not due to a central reduction in anxiety. den Boer, J.A. et al., Recent Developments in the Psychopharmacology of Social Phobia, Eur. Arch. Psychiatry Clin. Neurosci, **244:** 309-316 (1995). Beta-blockers have not been shown to be superior to a placebo in double-blind studies of performance anxiety and in studies of generalized social phobia (Jefferson (1995), page 19).

Beta-blockers have recognized adverse effects on the cardiovascular system, the pulmonary system (especially in asthmatics), the central nervous system and the metabolism (especially in diabetics). Hoffman, B.B., and Lefkowitz, R.J.,

Catecholamines, Sympathomimetic Drugs and Adrenergic Receptor Antagonists, pp. 239-240, in Hardman, J.G. et al., editors, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., McGraw-Hill, New York (1996). The adverse side effects and minimal efficacy in treating generalized social phobia severely limits the therapeutic potential of beta-blockers.

Several double-blind, placebo-controlled studies have demonstrated the acute efficacy of monoamine oxidase inhibitors (MAOI) in the treatment of social phobia. Marshall, R.D., et al., Medication Therapy for Social Phobia, J. Clin. Psychiatry, **55 (Suppl. 6)**: 33-37 (1994). Irreversible MAOI's can, however, produce a number of problematic side effects, such as hypertensive crisis (if dietary restrictions are not followed), insomnia, sexual dysfunction, postural hypotension and weight gain. Id. at 34. Newer reversible MAOI's have fewer side effects, but are less effective in treating social phobia (Id. at 34-35).

Serotonin selective reuptake inhibitors (SSRI's) such as fluoxetine have also been used to treat social phobia. Leibowitz, M.R., Pharmacotherapy of Social Phobia, J. Clin. Psychiatry, **54 (Suppl. 12)**: 31-35 (1993).

Studies of the neurobiology of social phobia in humans have produced contradictory results. Tancer has reviewed evidence from pharmacological challenge studies (Tancer, M. E., Neurobiology of Social Phobia, J. Clin. Psychiatry, **54 (Suppl. 12)**: 26-30 (1993)). In one study, a challenge of normal volunteers and of social phobia patients with levodopa produced the same changes, as measured by prolactin levels and rate of eyeblink. Id. at 29. No evidence of dopaminergic dysfunction was found in social phobia patients. Id. In contrast, Tancer found that the cortisol response to fenfluramine suggested that patients with social phobia may exhibit dysregulation in serotonergic neurotransmission (specifically, postsynaptic receptor supersensitivity), but have normal noradrenergic and dopaminergic activity. Id.

In general, SSRI have varying degrees of selectivity for 5-HT re-uptake by the presynaptic neuron compared to other aryl amine re-uptake transporters. While the basic mechanism of action is thought to involve inhibition of re-uptake of serotonin, the family of SSRI drugs also inhibit the re-uptake of norepinephrine and dopamine.

Other researchers are not so certain of the neurobiological condition underlying social phobia. Jefferson reviewed other studies in addition to those cited by Tancer, and concluded that the role of serotonin in the neurobiology of social phobia remains unclear. "In fact, no striking neurobiological or physiologic abnormality has been identified in social phobia." Jefferson, J.W., Social Phobia: Everyone's Disorder? J. Clin. Psychiatry, **57 (Suppl. 6)**: 28-32 (1996).

Miner and Davidson supported a serotonergic model of social phobia over a dopaminergic model. Miner, C. M. and Davidson, J. R. T., Biological Characterization of Social Phobia, Eur. Arch. Psychiatry Clin. Neurosci., **244:** 304-308 (1995). Miner and Davidson stated that to provide support for a dopaminergic pathology in social phobia, studies of dopamine agonists (e.g., bupropion, amantadine) would need to show efficacy in the disorder, and as of 1995, no such data existed. Id. at 306. These authors reviewed findings that they considered supportive of serotonergic involvement in the etiopathology of social phobia. Id.

Potts and Davidson stated earlier that the results in several treatment studies supported a dopaminergic theory for the etio-pathophysiology of social phobia. Potts N.L.S. & Davidson, J.R.T., Social Phobia: Biological Aspects and Pharmacotherapy, Prog. Neuro-Psychopharmacol. & Biol. Psychiat., **16:** 635-646 (1992). Potts and Davidson provided neither specific disclosure nor suggestion as to which dopaminergic pathway might be involved in social phobia, only citing for support a number of dopamine abnormalities seen in patients and pharmacotherapy studies. Id. at 643.

In general, the evidence suggests that reversible inhibitors of monoamine oxidase, such as moclobemide and brofaromine, hold some promise for safer and more acceptable pharmacotherapy of social phobia. Other drugs meriting study include venlafaxine and nefazodone, although their efficacy has not been established. Recent findings of abnormal brain dopamine reuptake site density in social phobia suggest that further investigation of dopaminergic drugs for treatment of social phobia may be warranted. A new area of research is the combination of psychotherapy and pharmacotherapy. Further work is needed to establish whether combination therapy is superior to a single modality, and if so, for which patients.

In summary, the neurobiological bases that underlie social phobia in humans are unknown at present. However, it is thought the mechanism underlying social phobia is regulated by the same structures of the brain engaged in other forms of appetitive behavioral processes.

Neurobiology of Social Phobia: Animal Models.

Animal models have been applied to various behavior models. The animal models have been used to measure various types of behavioral and psychological conditions including open field studies, feeding studies, and social interaction studies. Several animal models based at least partially on dopaminergic systems, including the nigrostriatal dopaminergic are especially relevant, including sexual interaction studies (Pomerantz, S.M., Apomorphine Facilitates Male Sexual

Behavior of Rhesus Monkeys, Pharm. Biochem. & Behav., **35:** 659-664 (1990)), social biological models for depression (Jones, I.H., et al., Toward A Sociological Model of Depression, A Marsupial Model, Brit. J. of Psychiatry, **166:** 475-479 (1995); Trulson, M.E., & Crisp, T., Behavioral and Neurochemical Effects of Apomorphine in the Cat, European J. Pharm., **80:** 295-309 (1982)) and models of psychosis (Davis, R.E., et al. Continuous Low-Level Apomorphine Administration Induces Motor Abnormalities and Hallucinogen-Like Behaviors, PsychoPharm, **85:** 1-7 (1985)).

A Neurobiological Model of Social Phobia.

Several lines of evidence support a dopaminergic model for social phobia. A recent report showed that patients having clinical social phobia disorder may have a dysfunction in the striatal dopaminergic system, specifically a deficit in dopamine uptake sites. Tiihonen, J., et al., Dopamine Reuptake Site Densities in Patients with Social Phobia, Am. J. Psychiatry, **154:** 239-242 (1997). This work supports earlier pharmacological research in this area that showed that where haloperidol, a known dopamine receptor antagonist, generally worsens the social phobic conditions as shown by an increase in the symptoms of the dysfunction. Mikkelsen, E.J., et al., School Avoidance and Social Phobia Triggered by Haloperidol in Patients with Tourette's syndrome, Am. J. Psychiatry, **138:** 1572-1576 (1981).

A dopaminergic model of social phobia is consistent with the actions of other drugs known to act on dopaminergic systems. Psychoactive drugs such as cocaine and amphetamines affect dopamine transmission by respectively blocking the re-uptake transporter and by depleting dopamine storage in the presynaptic neuron. Both of these drugs produce changes in socialization of individuals, and can induce clinical anxiety.

Three areas innervated by dopaminergic neurons are the mesolimbic system, the nigrostriatal system and the medial preoptic areas (FIGURE 1). The mesolimbic system has been identified as the system in the brain of mammals responsible for goal-oriented behavior.

The primary anatomic structures involved in processing and regulating goal-oriented behavior are the nucleus accumbens, habenula, amygdala, septum, olfactory tubercle, and the bed nucleus of the stria terminalis. The ventral tegmental area (VTA) of the midbrain interconnects and integrates these regions of the brain. Neurons connecting these structures to the VTA are predominantly dopaminergic. Björklund, A, & Lindvall, O., Dopamine- containing systems in the CNS, In: Handbook of Chemical Neuroanatomy, Vol. 2, Classical Transmitters in

the CNS, Part I, Björklund, A. & Hökfelt, T., eds., Elsevier, Amsterdam (1984) pp. 55-122.

Dopamine has been shown to have a role in drug and alcohol addiction, male sexual function, locomotion, and goal-oriented behavior in animals. Electrophysiological and neurochemical measurements of the extracellular concentration of dopamine in the VTA, the medial preoptic area of the hypothalamus, in the nucleus accumbens and the amygdala have clearly shown correlations between stimuli evoking behavior (e.g., sexual behavior) and an increase in dopamine levels (Hull, Elaine M., Dopaminergic influences on male rat sexual behavior, In: Neurobiological Effects of Sex Steroid Hormones, Erectile Dysfunction, Micevych, P.E. & and Hammer, R.P., eds., Cambridge University Press, Boston (1995)).

Studies have shown dopaminergic neurons related to such behavior to fall into three groups: tuberoinfundibular dopaminergic (TIDA) neurons, periventricular-hypophyseal dopaminergic (PHDA) neurons and incertohypothalmic dopaminergic (IHDA) neurons. Moore, K.E. & Lookingland, K.J., Dopaminergic neuronal systems in the hypothalamus, In: Psychopharmacology: The Fourth Generation of Progress, Bloom, F.E. & Kupfer, D.J., eds., Raven Press, New York (1995) pp. 245-256.y The primary focus on behavior regulation in the rat model has found the TIDA neurons to be significant.

In an animal model of social interaction, microelectrode measurements of extracellular dopamine in the nucleus accumbens and the VTA clearly show an increase following the three minute presentation of a second rat to the experimentally monitored rat. Cedarbaum, J.M. & Schleifer, L.S., Drugs for Parkinson's Disease, Spasticity, and Acute Muscle Spasms, Chapter 20, in Gilman, A.G., et al.. eds., Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th edition, Pergamon Press, New York (1990). The authors noted that apomorphine given i.v. at a dose of about 25 μg/kg to 50 μg/kg reduced extracellular dopamine in both these anatomical structures.

Dopamine receptors, classified pharmacologically into the groups D_1 through D_5, as well as the dopamine autoreceptor, have been studied. Kiyatkin, E.A., Functional Significance of Mesolimbic Dopamine, Neurosci. and Biobehav. Reviews, **19:** 573-598 (1995). Selective agonists and antagonists to the major dopamine receptors, D_1 and D_2 have been used to measure the effects of dopamine. The dopamine autoreceptor, found on the presynaptic dopaminergic nerve has been postulated in the regulation of dopamine transmission through the central nervous system. Dopamine released at the synaptic junction between the efferent and afferent neurons is either diffused into extracellular space, or metabolized, or taken up by the presynaptic neuron for reprocessing and/or metabolism.

Animals treated with dopamine D_2 antagonists such as haloperidol become more sensitive to dopamine and exogenous dopaminergic drugs. Gordon, J.J., & Diamond, B., Enhancement of Hypophysectomy-Induced Dopamine Receptor Hypersensitivity in Male Rats by Chronic Haloperidol Administration, J. Neurochem., **42:** 523-528 (1984). This behavior known as supersensitivity is seen with chronic administration of dopamine agonists, such as apomorphine. Bailey, R.C., & Jackson, D.M., A Pharmacological Study of Changes in Central Nervous System Receptor Responsiveness After Long-Term Dexamphetamine and Apomorphine Administration, Psychopharmacology, **56:** 317-326 (1978). The hyperactivity associated with challenge doses of apomorphine during chronic treatment is not fully understood.

SUMMARY OF THE INVENTION

A dopaminergic agonist such as apomorphine reduces the patient's inability to engage in social interactions that characterizes social phobia. Treatment regimens that achieve a target plasma concentration of the dopaminergic agonist in the range of about 0.5 ng/mL to about 10 ng/mL at C_{max} with chronic therapy of 2 or more treatments provide a therapeutically effective dose that produces amelioration of social phobia in a patient.

The dopaminergic agonist may be formulated as a sublingual tablet, buccal patch, intranasal formulation, transdermal composition or composition for intravenous injection. Suitable dopaminergic agonists are apomorphine, piribedil, bromocriptine, and the like.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings:

FIGURE 1 is a simplified diagram illustrating the relationships of the anatomical brain structures believed to be involved in social phobia;

FIGURE 2 is a graph showing the cumulative number of successful interactions accomplished by male rats receiving daily subcutaneous injections of vehicle alone (control) and apomorphine at either 0.2 mg/kg/day, 0.8 mg/kg/day or 2.0 mg/kg/day;

FIGURE 3 is a graph showing the percent of male rats showing signs of hyperactivity during chronic subcutaneous apomorphine treatment;

FIGURE 4 is a graph showing the C_{max} values measured in rats receiving chronic subcutaneous apomorphine on Day 1 and on Day 63; and

FIGURE 5 is a graph showing the area under the curve (AUC) values measured in rats receiving chronic subcutaneous apomorphine on Day 1 and on Day 63.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

A dopaminergic agonist such as apomorphine hydrochloride, formulated as a sublingual tablet, buccal patch, intranasal preparation, rectal suppository, transdermal drug, or given parenterally by intravenous or subcutaneous injection, ameliorates social phobia. The amelioration of social phobia is believed to be due to reduction in the fear response of avoidance and self-abusive tendencies of the patient suffering from social phobia.

Apomorphine is the preferred drug for the practice of this invention. However, other mixed dopamine agonists, D_1 dopamine receptor agonists, or D_2 dopamine receptor agonists may be used to modulate extracellular dopamine concentrations in a similar manner. In addition to apomorphine, illustrative agonists are piribedil, bromocriptine, lysergide, and pergolide.

The effective amount of dopaminergic agonist required for the amelioration of social phobia is a function of the potency of the substance on central nervous system dopamine receptors. In general, a therapeutically effective treatment of social phobia is associated with dosages and treatment regimens that achieve a target plasma concentration of apomorphine of about 0.5 ng/ml to about 10 ng/ml. Apomorphine is administered chronically with a single daily dose or multiple daily doses. The dosage level is dependent upon the bioavailability; for example, a bioavailability of about 10% to about 15% would require a dosage of about 30 mg/day to about 50 mg/day. Different routes of administration are associated with correspondingly different bioavailability. Thus, the target plasma concentration of apomorphine of about 0.5 ng/ml to about 10 ng/ml may be achieved by a sublingual dosage of apomorphine in the range of about 8 mg/day to about 60 mg/day. The same target plasma concentration may be achieved by intravenous injection of about 3 mg/day to about 5 mg/day. The amount of other dopamine agonists used is inversely proportional to the effectiveness of the agonist compared to apomorphine hydrochloride. Duration of treatment is at least about four weeks.

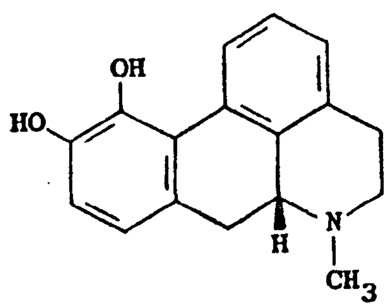
A preferred treatment regimen for apomorphine hydrochloride in sublingual tablet dosage form is a chronic administration of from about 4 to about 120 mg/day of apomorphine hydrochloride in single or multiple doses, administered daily for a time period of at least about four weeks, typically for a period of about six months to about twelve months.

Other dosage forms are also suitable for the administration of apomorphine. Transdermal formulations provide an effective mode of administering apomorphine; see, for example, U.S. Patent No. 5,562,917 to Durif et al., incorporated herein by reference. Apomorphine hydrochloride and the like can also be administered by subcutaneous injection at a dosage from about 0.002 mg/kg to

about 0.5 mg/kg in a single bolus injection or multiple injections. Continuous intravenous infusion at a rate of about 0.001 mg/kg/hour to about 4 mg/kg/hour is another suitable mode of administering apomorphine HCl.

A treatment regimen that comprises a combination of modes of administration is also suitable for the treatment of social phobia. Such treatment regimens include an initial subcutaneous injection followed by chronic treatment by administration via sublingual tablets. Alternatively, an initial subcutaneous injection can be followed by chronic treatment by administration of the active ingredient via a transdermal patch.

The chemical structure of the preferred active ingredient, apomorphine, is shown in Formula I below.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Apomorphine exists in a free base form or as an acid addition salt. For the purposes of the present invention, apomorphine hydrochloride is preferred; however, other pharmacologically acceptable moieties thereof can be utilized as well. The term "apomorphine" as used herein includes the free base form of this compound as well as the pharmacologically acceptable acid addition salts thereof. In addition to the hydrochloride salt, other acceptable acid addition salts are the hydrobromide, the hydroiodide, the bisulfate, the phosphate, the acid phosphate, the lactate, the citrate, the tartrate, the salicylate, the succinate, the maleate, the gluconate, and the like.

Additional preparations, such as conjunctival, rectal, iontophoretic, etc., as a means to deliver apomorphine are provided by the present invention. Formula and process variations such as the inclusion of ascorbic acid, glutathione, tocopherol, sodium metabisulfite or any other antioxidant acceptable for human or animal use and added to expressly preserve the drug substance are considered part of this invention. Sublingual and/or buccal formulations comprising those described by El-Rashidy et al. in U.S. Patent No. 5,624,677, incorporated by reference, may be useful considerations for delivering apomorphine by these routes.

In addition to apomorphine, other dopaminergic drugs may alternatively be used in a similar manner as the active ingredient in the practice of the present invention. Examples of such alternative active ingredients and suitable dosage forms are piribedil mesylate, e.g. in tablets for oral treatment (20 to 50 milligrams per tablet) as well as parenteral preparations of piribedil mesylate (3 mg/mL) and other dosage forms.

Animal models have been used to assess the utility of apomorphine in the treatment of social phobia. Since the outcome of a social phobic response to a stimulus is an avoidance activity, the effects of apomorphine have been examined on successful social interactions as measured by the frequency of mating in naive male rats treated with apomorphine hydrochloride.

EXAMPLE 1

Social Interaction Study

Male Sprague-Dawley CD rats, about six weeks old at the start of the study were housed individually in isolated cages. Dosage groups (0, 0.2, 0.8, and 2.0 mg/kg/day of apomorphine hydrochloride) of 24 rats per group were pre-conditioned for two weeks in a controlled environment having a photoperiod of 12 hours light and 12 hours darkness. The pre-conditioned rats were then chronically treated with morning daily subcutaneous injections of apomorphine hydrochloride prepared in a stabilizing vehicle once daily for four weeks prior to social interaction experimentation. The stabilizing vehicle was 0.75% NaCl aqueous solution containing 1% ascorbic acid and 0.05% sodium metabisulfite with a pH between 3.0 and 4.0 and aseptically filtered through a presteralized 0.22 μm membrane filter.

On the evening of the twenty-first day each male rat was caged together with a nulliparous female rat of the same strain that had been pre-conditioned for six weeks. Female rats were preconditioned to the same light / dark cycle synchronized to that of the male rats. No visual contact was made between rats of different genders prior to the experiment. No apomorphine was administered to the female rats.

Successful social interaction was defined as intercourse, which was determined by the presence of sperm in a vaginal smear taken the following morning. Mated females and the corresponding males were removed from the mating pool. This experiment was repeated with the remaining rats, with the same male interacting with the same female for a total of eight consecutive nights.

Table 1
Social Interactions (Intercourse) Between Paired Male and Female Rats

Social Interactions on Each Evening, Evenings 1 - 8 [Cumulative number]

Group	Dose mg/kg/day	Evening 1	2	3	4	5	6	7	8
1	0.0	4 [4]	3 [7]	6 [13]	5 [18]	3 [21]	1 [22]	1 [23]	1 [24]
2	0.2	9 [9]	3 [12]	9 [21]	1 [22]	1 [23]	0 [23]	0 [23]	0 [23]
3	0.8	7 [7]	5 [12]	6 [18]	3 [21]	0 [21]	1 [22]	0 [22]	1 [23]
4	2.0	12 [12]	3 [15]	4 [19]	2 [21]	1 [22]	0 [22]	1 [23]	0 [23]

The results of this study in male rats showed an increase in the frequency of successful social interactions with corresponding paired female rats following a period of four weeks of daily apomorphine treatment (Table 1, FIGURE 2). Half of the females were impregnated on the first night by males in the 2.0 mg/kg/day group, half were impregnated by the second night by rats in the lower dosage groups, but half of the females were not impregnated by males in the vehicle control group until the third night.

Mounting and copulation behaviors in the rat are directed to a great extent by the female and her estrous cycle. The normal rat estrous cycle period is about three to five days from estrous to estrous. The estrous period can be modified by external influences; for example, housing female rats in the same room, as in this case, would be expected to synchronize estrous cycles. Generally, only near or during estrous will female rats assume a copulatory position allowing the male to mount.

The data show greater success in social interactions after chronic apomorphine therapy. Since rats are about 5 to 20 times less sensitive to apomorphine than humans, the corresponding therapeutic dosage range for humans is from about 0.01 mg/kg/day to about 0.4 mg/kg/day.

EXAMPLE 2

Supersensitivity to Dopamine Induced by <u>Chronic Apomorphine Treatment</u>

Male Sprague-Dawley CD rats, were preconditioned as described in Example 1 for a period of two weeks. The pre-conditioned rats were placed into groups that received subcutaneous apomorphine hydrochloride in the same vehicle used in Example 1 at the doses of 0.1, 0.3, 0.8 and 2.0 mg/kg/day in addition,

vehicle alone (Placebo group) or were untreated (Control). Each dosage group consisted of 70 male rats. The fraction of the group involved in hyperactivity for each dosage group was recorded. Hyperactivity was defined as excessive stereotypic head movements (sniffing, licking or gnawing), circling, rearing, and thrusting in the cage.

No increase in hyperactivity was observed in rats of the Control or Placebo groups or in rats receiving apomorphine hydrochloride at 0.1 or 0.3 mg/kg/day. FIGURE 3 shows the increase in hyperactivity in the groups treated with apomorphine hydrochloride at 0.8 and 2.0 mg/kg/day. These data are consistent with an onset of supersensitivity of the dopaminergic systems occurring after about four to six weeks of treatment.

EXAMPLE 3

Pharmacokinetics of Apomorphine During Chronic Apomorphine Treatment

The pharmacokinetics of the drug was studied over a similar dosage range. Male rats were assigned to dosage groups of 32 rats. Each group received subcutaneous injections of apomorphine hydrochloride (0.8, 2 or 8 mg/kg/day) in the same vehicle used in Example 1.

Apomorphine was rapidly absorbed (t_{max} = 0.25 hour for each dose tested on each day) and rapidly eliminated ($t_{1/2}$ = 0.16 hour to 0.39 hour). Apomorphine showed no tendency to accumulate with daily dosing between Day 1 and Day 63.

Chronic exposure to apomorphine for 63 days produced a reduction in the C_{max} (FIGURE 4) that varied with the dose: reduced by about one-third at 0.8 mg/kg/day, by about one-half at 2 mg/kg/day, and by about 20 percent at 8 mg/kg/day. The bioavailable dose is directly proportional to the given dose (FIGURE 4).

The area under the curve (AUC) was relatively unaffected after 63 days of chronic apomorphine treatment (FIGURE 5).

The foregoing is intended to be illustrative of the present invention, but not limiting. Numerous variations and modifications of the present invention may be effected without departing from the true spirit and scope of the invention.

WE CLAIM:

1. A method for amelioration of social phobia, comprising the steps of

identifying a patient having need of such treatment; and administering to the patient a dopaminergic agonist for a time period of at least about four weeks and in a therapeutically effective amount sufficient to reduce symptoms of social phobia.

2. The method of claim 1 wherein dopaminergic agonist is apomorphine.

3. The method of claim 2 wherein the apomorphine is administered as a sublingual tablet.

4. The method of claim 2 wherein the apomorphine is administered transdermally.

5. The method of claim 2 wherein the apomorphine is administered by intravenous injection.

6. The method of claim 2 wherein the apomorphine is administered as a subcutaneous injection.

7. The method of claim 2 wherein the apomorphine is administered to provide a patient's plasma concentration of apomorphine of about 5 ng/ml to about 8 ng/ml.

8. A method for the amelioration of social phobia, comprising the steps of

identifying a patient having need of such treatment; and administering to the patient a therapeutically effective dose of a dopaminergic agonist which is a member of the group consisting of apomorphine, piribedil, bromocriptine, lysergide, and pergolide for a period of at least about four weeks.

9. The method of claim 8 wherein the dopaminergic agonist is administered as a sublingual tablet.

10. The method of claim 8 wherein the dopaminergic agonist is administered as transdermally.

11. The method of claim 8 wherein the dopaminergic agonist is administered by intravenous injection.

12. The method of claim 8 wherein the dopaminergic agonist is administered as a subcutaneous injection.

13. The method of claim 8 wherein the dopaminergic agonist is apomorphine.

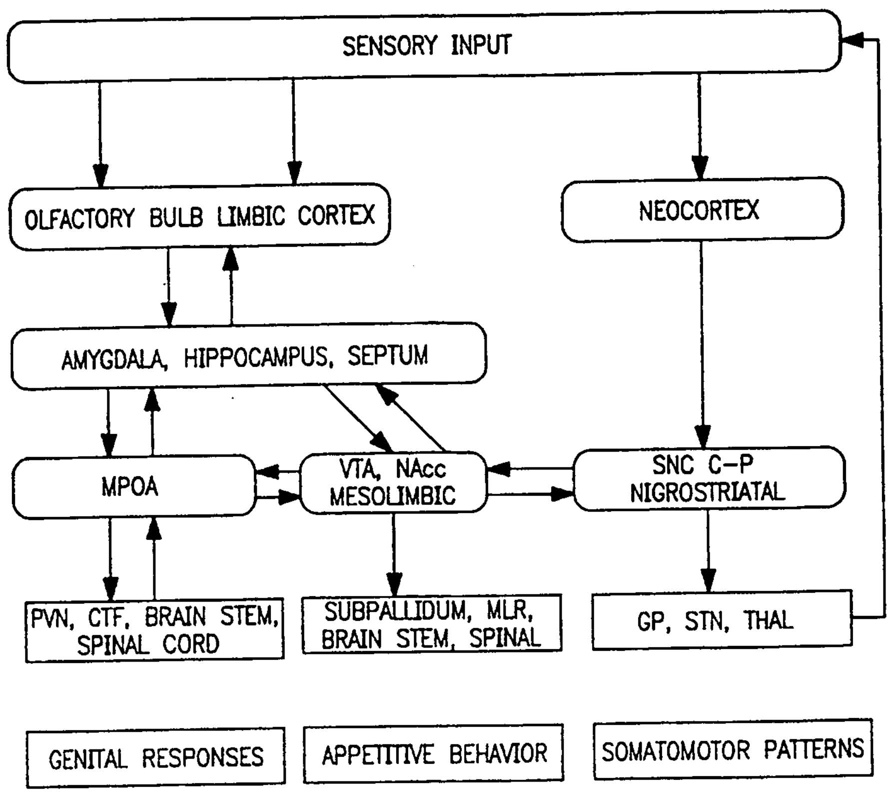
SENSORY INPUT
OLFACTORY BULB LIMBIC CORTEX
NEOCORTEX
AMYGDALA, HIPPOCAMPUS, SEPTUM
MPOA
VTA, NAcc
MESOLIMBIC
SNC C-P
NIGROSTRIATAL
PVN, CTF, BRAIN STEM,
SPINAL CORD
SUBPALLIDUM, MLR,
BRAIN STEM, SPINAL
GP, STN, THAL
GENITAL RESPONSES
APPETITIVE BEHAVIOR
SOMATOMOTOR PATTERNS

FIG. 1

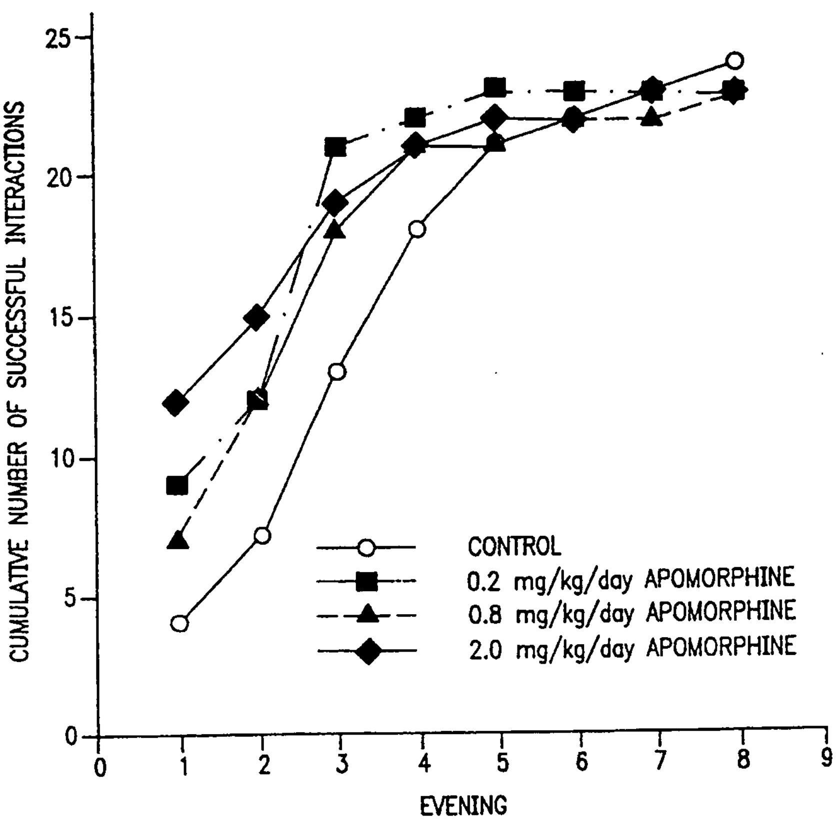
25
20
15
10
5
0
CUMULATIVE NUMBER OF SUCCESSFUL INTERACTIONS
0
1
2
3
4
5
6
7
8
9
EVENING
CONTROL
0.2 mg/kg/day APOMORPHINE
0.8 mg/kg/day APOMORPHINE
2.0 mg/kg/day APOMORPHINE

FIG. 2

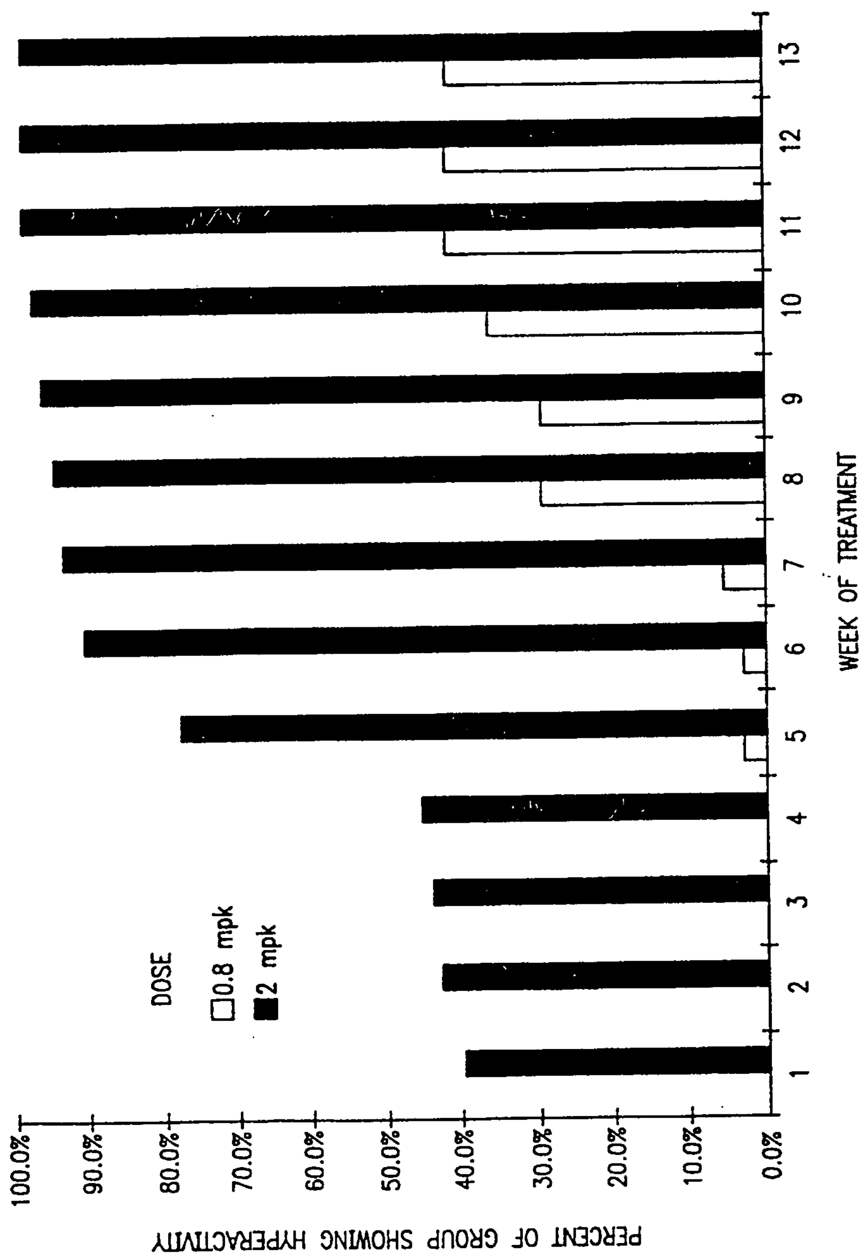
DOSE
0.8 mpk
2 mpk
PERCENT OF GROUP SHOWING HYPERACTIVITY
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
1
2
3
4
5
6
7
8
9
10
11
12
13
WEEK OF TREATMENT

FIG. 3

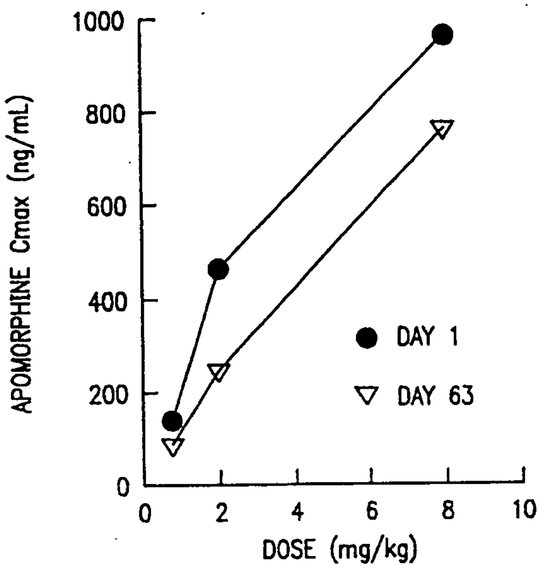
1000
800
600
400
200
0
APOMORPHINE Cmax (ng/mL)
0
2
4
6
8
10
DOSE (mg/kg)
DAY 1
DAY 63

FIG. 4

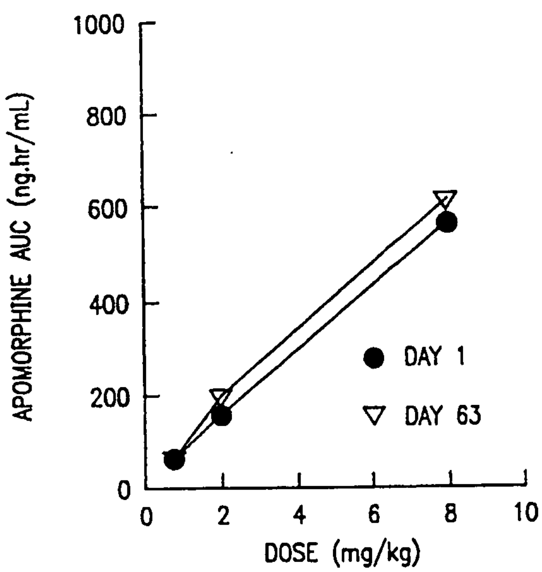
1000
800
600
400
200
0
APOMORPHINE AUC (ng.hr/mL)
0
2
4
6
8
10
DOSE (mg/kg)
DAY 1
DAY 63

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/17210

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A01N 43/42
US CL : 514/253, 282, 284, 288
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/253, 282, 284, 288

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, CAS, GPIC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HJORTH et al. Anticonflict Effects of Low Doses of the Dopamine Agonist Apomorphine in the Rat. Pharmacology Biochemistry & Behavior. 1986, Vol. 24, pages 237-240, especially pages 237 and 238.	1-13
Y	US 5,562,917 A (DURIF et al) 08 October 1996, col. 2, lines 37-47 and col. 1, lines 57-65.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 SEPTEMBER 1998	19 OCT 1998

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